Remarks/Arguments

Claims 39-43 are presently pending in this application and remain rejected. Claim 39 has been amended to recite an "isolated" antibody, which applicants always considered was their invention. Applicants thank the Examiner for withdrawal of some rejections. The remaining rejections to the claims are respectfully traversed.

Claim Rejections - 35 USC § 101 and 35 USC § 112, first paragraph

Claims 39-43 remain rejected under 35 U.S.C. §101 for lack of utility. The Examiner asserts that "the rejection is made for lack of a specific and substantial utility that does not require further experimentation to identify a real world use for the claimed invention." Applicants respectfully traverse the rejection.

The Examiner maintained the rejection and contends that (1) "it is not likely that one of skill in the art could reasonably predict based upon the primary sequence of SEQ ID NO: 255 what specific activity PRO302 may have" (page 4, lines 1-2). The Examiner cites Berendsen *et al.*, Galparin *et al.* and Attwood *et al.* for support; (2) "(w)hile the specification concludes that PRO302 protein can induce vascular permeability in the guinea pig model, it does not give the **actual data** or an indication of the relative activity of the PRO302 protein compared to the positive control" (page 5, lines 2-5); (3) the Fong Declaration and the art submitted by the Applicants (Dvorak *et al.*, Connolly *et al.*, Olander *et al.*, and Keck *et al.*) are not persuasive in showing that a positive result in the Miles assay alone was sufficient to support a well-established utility for a polypeptide" (page 12, 17-19).

A. Arguments

The Legal standards for Utility were discussed in the previous response filed 19 September, 2005.

"it is not likely that one of skill in the art could reasonably predict based upon the primary sequence of SEQ ID NO: 255 what specific activity PRO302 may have" (page 4, lines 1-2). The Examiner cites Berendsen et al., Galparin et al. and Attwood et al. for support;

The instant application discloses that PRO302 is a novel polypeptide that increases **vascular permeability**, and not as a proinflammatory molecule. Based on the positive results

obtained in the vascular permeability assay, Applicants had asserted a **specific and substantial** role for antibodies to PRO302 in stopping vascular leakage in diseases like in pulmonary leakage, capillary leakage, tumor leakage or burns. Applicants do not rely on homology data for utility of PRO302 hence any rejections, based on the teachings of Berendsen *et al.*, Galparin *et al.* and Attwood *et al.* are not relevant here.

"(w)hile the specification concludes that PRO302 protein can induce vascular permeability in the guinea pig model, it does not give the ***actual data*** *or an indication of the relative activity of the PRO302 protein compared to the positive control" (page 5, lines 2-5)*;

These remarks are a clear indication that the Examiner applies a standard that might be appropriate if the issue at hand were the regulatory approval for PRO302 as a drug, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA, reviewing an application for a new drug molecule will indeed ask for actual numerical data, statistical analysis, and other specific information before a drug is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards of market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Indeed, in *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980), the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. The identification of a diagnostic utility for a compound should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

Applicants respectfully submit that PRO302's utility lies in its use as a target for the development of anti-vascular leakage agents. Based on the 'well-established' utilities for vascular permeability factors in the art as a whole, one skilled in the art would know how to use PRO302 (polypeptides and nucleic acids thereof), or anti-PRO302 antagonists (antibodies) to stop vascular leakage in a variety of diseased conditions such as, pulmonary leakage, capillary leakage, tumor leakage, or in burns, at the time of the effective filing date of September 14, 1998. Human VEGF (a well-known molecule that causes vascular permeability) at 0.1 μg / 100 μl was

used as a positive control, inducing a response of 15-23 mm diameter (see Example 85 (page 215-216 of instant specification).

The Fong Declaration and the art submitted by the Applicants (Dvorak et al., Connolly et al., Olander et al., and Keck et al.) are not persuasive in showing that a positive result in the Miles assay alone was sufficient to support a well-established utility for a polypeptide" (see for example, page 12, line 17-19)

Applicants filed an executed Declaration by Sherman Fong, Ph.D. that discussed the vascular leakage assay and how this assay identifies molecules that induce leakage, the mechanism of vascular leakage/permeability, how the assay and its modifications have been widely used in the art by several investigators to identify well-established leak inducing molecules like VEGF (VPF) etc. and thereby determine specific uses for anti-VEGF. Applicants submitted a positive exemplary exhibit of which is shown in Exhibit I attached with the Declaration to show that molecules like PRO302 induce and display blemishes of a previously injected marker dye due to vascular leakage, which is measured in the "guinea pig vascular leak assay".

Applicants further presented exemplary patents Dvorak *et al.*, U.S. patent 4,456,550, issued June 26, 1984; Connolly *et al.*, U.S. patent 5,008,196, issued April 16,1991; Olander *et al.*, U.S. patent 5,036,003 issued July 30, 1991; and Keck *et al.*, U.S. patent 5,240,848 issued August 31, 1993 that together showed that the knowledge available in the art as a whole, for vascular permeability factors, was correlated with diseases well before the time of effective filing date of the instant application and these patents also provide a nexus between utility as a vascular permeable factor and the diseased state. Applicants submitted that based on positive results for PRO302 in the well-established vascular permeability assay, which in turn has been correlated with "well-established utilities" in the art as a whole, a nexus between PRO302 utility and 'usefulness in disease' would be known to one skilled in the art. The skilled artisan would know how to use PRO302 polypeptides, or anti-PRO302 antagonists (antibodies) to stop vascular leakage in diseased conditions such as, pulmonary leakage, capillary leakage, tumor leakage, or in burns, at the time of the effective filing date of September 14, 1998.

Thus, Applicants maintain that they have provided at least one "well-established utility" for PRO302 antibodies that would be considered specific, credible and substantial by one skilled

in the art. Example 85 of the present application provides detailed protocols for the (guinea pig vascular permeability) GVP assay, including the extensive step-by-step guidance in the specification. By following the disclosure in the specification, one skilled in the art would know that PRO302 polypeptide is capable of inducing vascular leakage or permeability and would know how to use PRO302 and its antibodies without undue experimentation, as discussed above.

Accordingly, Applicants believe that the present rejection under 35 U.S.C. §101 and §112, first paragraph would be withdrawn.

Claim Rejections - 35 USC § 101

Claim 39 was rejected under 35 U.S.C. §101 because the claimed invention was allegedly directed to non-statutory subject matter.

Applicants have amended Claim 39 to recite an "isolated" antibody, support for which can be found in the instant specification at least on page 73, line 27-36. Accordingly, Applicants respectfully request that this rejection under 35 U.S.C. §101 be withdrawn.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C40). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: April 25, 2006

Daphne Reddy

Daphne Reddy
Reg. No. 53,507

HELLER EHRMAN LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638